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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,471	09/01/2006	Elliot Ehrich	2685.3002 US	4421

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EXAMINER	
POLANSKY, GREGG	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,471	EHRICH ET AL.	
	Examiner	Art Unit	
	GREGG POLANSKY	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10-16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10-16 and 18-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. In view of the Appeal Brief filed on 8/24/2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614.

2. Applicants' Information Disclosure Statement, filed 1/21/2009, is acknowledged and has been reviewed.

3. The following rejections are newly applied. They constitute the complete set presently being applied to the instant application.

4. Claims 1, 2, 4-8, 10-16, and 18-28 are pending and presently under consideration.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1, 2, 4, 5, 22-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al. (*Ibid.*), in view of Richards et al. (U.S. Patent Application Pub. No. 2003/0158176) and Levin et al. (The American Journal of Medicine, 1996, Vol. 100, Sup. 1, pp. S40-S48, Abstract only).

Freund et al. teach aqueous aerosols of *inter alia* anticholinergic agents, including trospium chloride and ipratropium bromide (*see* page 2, paragraphs 20, 21 and 23), and betamimetics, including formoterol, salbutamol, and fenoterol (see page 2, paragraphs 36 and 37) for inhalation in the treatment of respiratory passage diseases (*see* page 1, paragraph 7 and page 3, claim 2). The reference teaches the active ingredients can be used singly or in combination. Freund et al. also teach an active agent concentration range of 10mg/100ml to 20000mg/100ml and a nebuliser delivering 12 microliters of concentrate per operation (*see* page 3, paragraph 52). Therefore, the dose of active agent would be between 1.2 mcg and 2400 mcg per operation.

The duration of action of the trospium formulations are dose dependent. Accordingly, the relationship of the dose of trospium to the duration of action is a characteristic of trospium. Since Freund et al. teach a dose range which encompasses the instantly claimed dose range, the duration of action of trospium taught by Freund et al. would be the same as that of the instant invention.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Also see *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the

process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate).

Applicants argue that trospium is taught by Freund et al. amongst a list of over 100 different and diverse drugs and that trospium is not specifically exemplified.

A reference that clearly names the claimed species anticipates the claim no matter how many other species are named. A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte* A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter.1990). In instant case, the instantly claimed trospium is disclosed by Freund et al. in a short list of 4 anticholinergic agents. The instantly claimed formoterol is disclosed by Freund et al. in a short list of 4 betamimetics.

Levin et al. teach administration of an anticholinergic agent in combination with a β2 agonist in the treatment of COPD. The anticholinergic agent (ipratropium, **500 micrograms**) and the β2 agonist (albuterol/salbutamol, 2.5 mg) are administered by inhalation using a small volume nebuliser, according to Levin et al. The combination produced a greater therapeutic effect than the agents administered separately. See Abstract. Ipratropium is one of the 4 anticholinergics disclosed by Freund et al. (which also includes the instantly claimed trospium). Albuterol (also called salbutamol) is one of the 4 betamimetics disclosed by Freund et al. (which also includes the instantly claimed formoterol).

Richards et al. teach anticholinergic (antimuscarinic) agents, including the compound, trospium, are useful for the treatment of acetylcholine-mediated disorders, in particular, the treatment of *inter alia* chronic obstructive pulmonary disease (COPD) and asthma (*see* page 5, paragraphs 91 and 93). Richards et al. teach the advantageous administration of anticholinergic agents by inhalation or insufflation in the form of an aerosol or a dry powder (administered by dry powder inhaler (*see* page 6, paragraphs 103 and 106). Richards et al. teach that dose of anticholinergic agents depends on many factors, including the potency of the compound, the age and weight of the patient and the severity of the condition (*see* page 6, paragraph 105). One of ordinary skill in the art would have optimized the doses taught by Freund et al. and Levin et al. to maximize the therapeutic effects, including duration of action, and minimize the deleterious effects of the active agent.

One of ordinary skill in the art (e.g., a pulmonologist) would have found it obvious to combine these three teachings to treat diseases such as COPD and asthma by local (i.e., inhalation) administration of trospium and an additional agent, such as formoterol. Levin et al. teach the usefulness of treating COPD with a combination of (by inhalation) an anticholinergic agent (ipratropium) and a β2 agonist (salbutamol). Freund et al. teach the usefulness of *inter alia*, anticholinergics and betamimetics (including trospium and formoterol, respectively) for treating respiratory passages diseases and Richards et al. teach COPD and asthma as two respiratory diseases effectively treated by trospium. One would have been motivated to administer the active agents via inhalation to directly target the respiratory system, thereby minimizing the amount of active agents

administered systemically, thus avoiding excessive systemic absorption and resulting undesirable systemic effects, and to improve upon the known methods of treatment for COPD and asthma. One of ordinary skill in the art would have found it obvious to substitute one known element (e.g. trospium) for another (e.g. ipratropium).

7. Claims 1, 2, 4-8, 10-16, and 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al. (*supra*), in view of Richards et al. (*supra*), as applied to Claim 1, 2, 4, 5, 22-26 and 28 above, and further in view of Bernstein et al. (U.S. Patent Application Pub. No. 2004/0105821 A1).

Bernstein et al. teach particulate sustained release pharmaceutical formulations for inhalation administration. See Abstract. The sustained release dry powder formulations are disclosed to be useful in the treatment of respiratory disease, including *inter alia* asthma and COPD. Further, the sustained release formulation provides local or plasma concentrations at nearly constant values over the intended period of release (for example, up to 2 to 24 hours), allowing patients to take treatments once or twice daily. See page 13, paragraphs 184, 189 and 190. Bernstein et al. teach anticholinergic agents (such as ipratropium bromide) and bronchodilator/sympathimetic agents (such as formoterol) may be formulated by the methods disclosed. See pages 8-9, paragraphs 92 and 123. Although Bernstein et al. do not teach trospium *per se*, they do teach anticholinergic agents in general. Freund et al. also teach anticholinergic agents can be administered by dry powder formulation, as well as specifically teaching both ipratropium bromide and trospium. One of ordinary skill in the art at the time of the

invention would have understood (especially in light of the teaching of Freund et al.) that one known anticholinergic agent (i.e., trospium) could be substituted for another (i.e., ipratropium) with a reasonable expectation of success. The formulations disclosed by the reference utilize spray drying techniques. See page 10, paragraph 148, and page 11, paragraphs 159-162. The aerodynamic diameter of the formulation is adjusted to enable particle deposition by inhalation to the region of interest in the lung. See pages 4-5, paragraphs 44 and 52. Particles taught by Bernstein et al. have a volume average diameter and volume median diameter of between 1 and 5 microns, and a tap densities ranging from 0.22 to 0.68 g/mL, and at least 50% by weight of the microparticles delivered to the lung is delivered to the central and upper lung; these disclosures satisfy the requirements of instant Claims 8, 9, 11, and 12. See page 5, paragraph 57; page 14, Table 1; and page 15-16, claims 4, 5 and 21. The reference teaches the inclusion of surfactants (e.g., lipids), including phospholipids and bulking agents (e.g., amino acids), including leucine, in the formulations. See page 2, paragraph 14; page 6, paragraph 68; page 10, paragraphs 143 and 144; and pages 15-16, claims 10 and 31. The surfactants comprise less than 10% by weight of the microparticles and 0.1 to 5% of the formulation. See page 7, paragraph 79 and page 12, paragraph 171. The active pharmaceutical agent is present from about 5 to 50 wt %. See page 9, paragraph 138. One would presume the remainder of the formulation (i.e., about **45—90 wt %**) would by comprised of the bulking agent (e.g., **leucine**).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the above 4 references to create an effective treatment for

respiratory diseases, such as COPD, that was administered by inhalation to target the lungs and reduce undesirable systemic effects, and long lasting so as to allow for once daily administration. The reference to Levin et al. teaches the therapeutic benefit of administration by inhalation of the combination of ipratropium (an anticholinergic agent) and salbutamol (a β2 agonist) in the treatment of COPD. Freund et al. and Richards et al. teach suitable therapeutic agents and routes of administration for treating COPD and asthma, and Bernstein et al. teach methods for creating sustained release formulations of active agents suitable for treating respiratory conditions, including COPD. One would have been motivated combine the teachings to improve upon the known methods of treatment for these respiratory diseases. As discussed above, the relationship of the dose of trospium to the duration of action is a characteristic of trospium.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 8 and 9-16 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 63-69, 76-84, 92-94, and 96-98 of copending Application No. 10/392333. Although the conflicting claims are not identical, they are not patentably distinct from each other because both drawn to similar dry powder compositions comprising trospium and the administration of the compositions by inhalation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. Claims 1, 2, 4-8, 10-16, and 18-28 are rejected.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614